

# Muscle wasting as an independent predictor of survival in patients with chronic heart failure

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## Abstract

**Background** Skeletal muscle wasting is an extremely common feature in patients with heart failure, affecting approximately 20% of ambulatory patients with even higher values during acute decompensation. Its occurrence is associated with reduced exercise capacity, muscle strength, and quality of life. We sought to investigate if the presence of muscle wasting carries prognostic information.

**Methods** Two hundred sixty-eight ambulatory patients with heart failure (age  $67.1 \pm 10.9$  years, New York Heart Association class  $2.3 \pm 0.6$ , left ventricular ejection fraction  $39 \pm 13.3\%$ , and 21% female) were prospectively enrolled as part of the Studies Investigating Co-morbidities Aggravating Heart Failure. Muscle wasting as assessed using dual-energy X-ray absorptiometry was present in 47 patients (17.5%).

**Results** During a mean follow-up of  $67.2 \pm 28.02$  months, 95 patients (35.4%) died from any cause. After adjusting for age, New York Heart Association class, left ventricular ejection fraction, creatinine, N-terminal pro-B-type natriuretic peptide, and iron deficiency, muscle wasting remained an independent predictor of death (hazard ratio 1.80, 95% confidence interval 1.01–3.19,  $P = 0.04$ ). This effect was more pronounced in patients with heart failure with reduced than in heart failure with preserved ejection fraction.

**Conclusions** Muscle wasting is an independent predictor of death in ambulatory patients with heart failure. Clinical trials are needed to identify treatment approaches to this co-morbidity.

**Keywords** Wasting; Sarcopenia; Cachexia; Heart failure; Survival

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## Introduction

Heart failure (HF) has huge socio-economic impact and is associated with high morbidity and mortality. Likewise, patients often present with reduced quality of life and low exercise

capacity as can be directly measured or extrapolated from breathlessness and fatigability. In addition, most patients present with co-morbidities that directly or indirectly worsen exercise tolerance, morbidity, and/or mortality. Among these, atrial fibrillation, diabetes mellitus, chronic obstructive

pulmonary disease, sleep-disordered breathing, iron deficiency, and chronic kidney disease play important roles. Recently, skeletal muscle wasting has emerged as an important co-morbidity of HF<sup>1</sup> that affects both patients with HF with preserved ejection fraction (HFpEF) and those with HF with reduced ejection fraction (HFrEF) in that it further reduces low peak oxygen consumption, 6 min walk distance, and handgrip as well as quadriceps strength.<sup>2–4</sup> The prevalence of skeletal muscle wasting has been reported to be 19–52% among all patients with HF. The large range mirrors the association with the cohort under investigation. For example, stable ambulatory patients seem to have lower prevalence values than patients with acute or advanced HF,<sup>5–7</sup> and patients with dilated cardiomyopathy may have higher prevalence values than patients with ischaemic heart disease.<sup>2,3,8</sup>

It is important to note that skeletal muscle wasting, in geriatric populations commonly called sarcopenia, is different from cachexia, because only cachexia is by definition associated with weight loss.<sup>4</sup> Recent data have shown that cachexia in patients with HF, usually termed cardiac cachexia, can be associated with skeletal muscle wasting; however, this is not a prerequisite, because also fat tissue and bone mineral density can be diminished during these catabolic wasting processes.<sup>9</sup> Reduced exercise performance, however, is primarily present in those patients who have lost skeletal muscle.<sup>10</sup> This finding coincides with reduced peripheral blood flow in patients with muscle wasting.<sup>11</sup> Interestingly, mitochondrial energy production can be improved in the skeletal muscle by intravenous iron therapy in patients with iron deficiency,<sup>12</sup> underlining the importance of iron provision for energy production in this system. Treatment of muscle wasting and iron deficiency may provide an interesting means to improve exercise capacity and quality of life, both of which are difficult to increase using guideline-recommended HF treatments.<sup>12</sup>

It has long been established that cardiac cachexia is associated with reduced survival, and this finding is independent of other prognostic factors such as age, reduced peak oxygen consumption, left ventricular ejection fraction (LVEF), or New York Heart Association (NYHA) class.<sup>13</sup> The aim of the present analysis from the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) was to test whether skeletal muscle wasting itself carries prognostic information in patients with HF, irrespective of whether HFrEF or HFpEF is present.

## Methods

### Study population

Patients were prospectively enrolled as part of SICA-HF at the Department of Cardiology, Charité Medical School, Campus Virchow-Klinikum, Berlin, Germany, between February 2010

and March 2014. All subjects provided written informed consent before being enrolled. The local ethics committee approved the study, which was funded by the European Commission's Seventh Framework Programme (FP7/2007–2013) under Grant Agreement Number 241558. All principles of the Declaration of Helsinki were fulfilled. Clinical data from this dataset have been published before and have served to characterize body composition as well as clinical features of patients with wasting disorders in HF.<sup>2,3,11</sup>

The inclusion criteria of SICA-HF were broad and have been published before.<sup>14</sup> In brief, patients were eligible if the following criteria were met: age >18 years, clinical signs and symptoms of chronic HF with LVEF ≤ 40% (HFrEF) or with an LVEF > 40%, and a left atrial dimension ≥ 4.0 cm (HFpEF). Exclusion criteria embraced previous heart transplantation, cardiac or embolic events within 6 weeks prior to the baseline examination, and patients on haemodialysis or with known pregnancy. Transthoracic two-dimensional echocardiography was performed before entering the study to assess standard cardiac parameters including LVEF using Simpson's biplane technique. Blood was drawn for serum and plasma sampling early in the morning after an overnight fast and after at least 15 min of supine rest. In addition, standard parameters were assessed including a full blood count and routine clinical biochemistry parameters.

### Definition of wasting

All patients underwent standardized procedures to assess muscle mass and body weight. Dual-energy X-ray absorptiometry (DEXA) was used to assess body composition. Like in previous publications from this dataset, muscle wasting was defined according to previously published criteria suggested to diagnose sarcopenia,<sup>15</sup> that is, an appendicular skeletal muscle mass 2 SDs below the mean of a healthy young reference group aged 18–40 years. This translates into an appendicular skeletal muscle mass below 7.26 kg in men or 5.45 kg in women.<sup>16</sup> Appendicular lean mass was defined as the lean mass of both arms and legs combined. Lean mass data from DEXA scan were evaluated, and the patients' muscle mass index was calculated.<sup>17</sup> This index assesses appendicular skeletal muscle mass (ASM in kg), calculated as the lean muscle mass of both arms and legs divided by height (in m) squared.<sup>18</sup> A DEXA scanner model 'lunar prodigy' was used with 'lunar en Core 2002' software (both from GE Medical Systems, Madison, WI, USA). Body weight was assessed after an overnight fast wearing light clothing without shoes on standardized weighing scales.

### Clinical biochemistry

Iron deficiency was defined as recommended in the guidelines of the European Society of Cardiology as serum ferritin

<100 ng/mL or serum ferritin 100–299 ng/mL with transferrin saturation <20%. N-terminal pro B-type natriuretic peptide was assessed on the Elecsys system using Roche assays (Roche, Basel, Switzerland). The glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula.

## Survival

Patients were followed until August 2018 when the database was censored and for a mean of  $67.2 \pm 28.0$  months or until death. All survivors were followed for at least 100 months.

## Statistical analysis

Baseline characteristics are expressed as mean  $\pm$  standard deviation or as number of patients with percentage. Unpaired Student's *t*-test and Fisher's exact test were used to analyse the difference between groups. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was not normally distributed and therefore transformed by logarithm of 10 in order to achieve normal distribution. To estimate the influence of risk factors, Cox proportional hazard analysis was performed, firstly as single-predictor (or unadjusted) model und subsequently as multivariate (or adjusted) model. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (IBM SPSS Statistics Version 25, IBM Corporation, Armonk, NY, USA). We considered a two-tailed *P*-value <0.05 as statistically significant.

## Results

### Study population

A total of 268 patients were enrolled, 87 of whom had HFpEF and 181 had HFrEF. The majority of patients were male; however, the proportion of female vs. male was higher in patients with HFpEF than in HFrEF (*Table 1*). Most patients had ischaemic heart disease and were in NYHA Classes II and III. Co-morbidities were highly prevalent; in particular, patients had a high prevalence of diabetes mellitus (41%), hypertension (81%), and atrial fibrillation (38%); 61.3% of patients with HFrEF had received a device implantation as detailed in *Table 1*; as expected, this proportion was significantly lower among patients with HFpEF.

Muscle wasting was present in 47 patients (17.5%), 39 of whom had HFrEF and 8 of whom had HFpEF (*P* = 0.016). Overall, patients with muscle wasting were older, were more likely to be male, had a higher NT-proBNP value, were more likely to be iron deficient, and were more likely to be anaemic (*Table 2*). No major difference was detected for kidney

function between patients with vs. without muscle wasting, but patients with muscle wasting tended to be more symptomatic as highlighted by a trend towards higher NYHA class (*Table 2*). More than 50% of the overall population were found to be iron deficient being present in 95 of 181 patients with HFrEF (52.5%) and in 42 of 87 patients with HFpEF (48.8%, *P* = 0.6).

### Survival analysis

A total of 95 patients (35.5%) died during a mean follow-up of  $67.2 \pm 28.02$  months, 25 (9.3%) of whom had muscle wasting. Kaplan–Meier analyses for mortality revealed a 12 month mortality rate of 4.9% [95% confidence interval (CI) 2.16–7.64%] and a 24 month mortality rate of 12.2% (95% CI 8.08–16.32%). This proportion was significantly higher in patients with muscle wasting: Kaplan–Meier analyses for mortality revealed a 12 month mortality rate of 11.11% (95% CI 1.89–20.3%) in patients with muscle wasting compared with 3.5% (95% CI 0.95–6.05%) and a 24 month mortality rate of 22.22% (95% CI 10.05–34.35%) in comparison with 10% (95% CI 5.89–14.12%) in those without (*P* = 0.003, *Figure 1*). Not surprisingly, survivors had a lower mean NT-proBNP of  $885.5 \pm 1630$  ng/L as compared with  $2374.6 \pm 3389.1$  ng/L in non-survivors (*P* = 0.001).

Several baseline variables were investigated with regard to their impact on all-cause death using single-predictor Cox proportional hazard analysis: age, NYHA class, LVEF, serum creatinine, NT-proBNP, the presence of iron deficiency, and the presence of muscle wasting all predicted survival (*Table 3* and *Figure 1*) and were entered into a multivariable model. After adjusting for all the aforementioned variables, LVEF, serum creatinine, and the presence of muscle wasting remained independent predictors of death. Splitting the models according to the presence of HFpEF or HFrEF showed that in patients with HFpEF, serum creatinine remained the only independent predictor of death, whereas in patients with HFrEF, LVEF and muscle wasting remained independent predictors of death; however, in this model, also a trend existed towards significance for advancing age (*Table 3*). Kaplan–Meier survival curves were constructed for illustrative purposes and showed an early separation of the survival lines (*Figure 1*).

## Discussion

We show here that skeletal muscle wasting, as defined using the cut-off values for sarcopenia, is an independent predictor of death in a mixed cohort of patients with HF. This effect was predominantly driven by patients with HFrEF who represented the majority of patients under study in the present analysis. In patients with HFpEF, the minority of patients with

**Table 1** Baseline characteristics of the study population

	All patients (n = 268)	HFpEF (n = 87)	HFrEF (n = 181)	P-value
<b>Baseline demographics</b>				
Age (years)	67.14 ± 10.86	68.48 ± 11.33	66.49 ± 10.61	0.16
Sex (% female)	57 (21.3%)	29 (33.3%)	28 (15.5%)	<b>0.001</b>
Aetiology (% ischaemic)	162 (60.4%)	40 (46%)	122 (67.4%)	<b>&lt;0.001</b>
BMI (kg/m <sup>2</sup> )	28.95 ± 5.03	30.35 ± 4.94	28.27 ± 4.94	<b>0.001</b>
Systolic blood pressure (mmHg)	127.43 ± 22.94	138.86 ± 22.88	121.87 ± 20.86	<b>&lt;0.001</b>
Diastolic blood pressure (mmHg)	75.04 ± 12.55	78.34 ± 13.49	73.43 ± 11.78	<b>0.003</b>
Heart rate (b.p.m.)	65.12 ± 10.76	63.69 ± 11.30	65.82 ± 10.45	0.14
LVEF (%)	39.00 ± 13.25	55.29 ± 5.96	31.17 ± 7.31	<b>&lt;0.001</b>
NYHA class	2.32 ± 0.63	2.17 ± 0.66	2.39 ± 0.60	<b>0.007</b>
<b>Medical history and co-morbidities</b>				
Diabetes mellitus (%)	109 (41.3%)	40 (47.6%)	69 (38.3%)	0.18
Hypertension (%)	214 (80.8%)	77 (90.6%)	137 (76.1%)	<b>0.005</b>
Previous myocardial infarction (%)	129 (49.6%)	23 (26.7%)	106 (61%)	<b>&lt;0.001</b>
Previous percutaneous intervention (%)	126 (48.8%)	32 (36.8%)	94 (55%)	<b>0.008</b>
Previous CABG procedure (%)	54 (21.1%)	12 (14.1%)	42 (24.6%)	0.07
Atrial fibrillation (%)	101 (38.1%)	26 (30.2%)	75 (41.9%)	0.08
Muscle wasting (%)	47 (17.5%)	8 (9.2%)	39 (21.5%)	<b>0.02</b>
Iron deficiency (%)	137 (51.3%)	42 (48.8%)	95 (52.5%)	0.6
Anaemia (%)	81 (30.2%)	22 (25.3%)	59 (32.6%)	0.26
Cachexia (%)	52 (20.2%)	10 (11.8%)	42 (24.3%)	<b>0.021</b>
Device implantation (%)	125 (46.6%)	14 (16.1%)	111 (61.3%)	<b>&lt;0.001</b>
ICD (%)	56 (44.8%, n = 125)	2 (14.3%, n = 14)	54 (48.6%, n = 111)	<b>0.02</b>
CRT-P or CRT-D (%)	50 (40%, n = 125)	5 (35.7%, n = 14)	45 (40.5%, n = 111)	0.78
Pacemaker (%)	19 (15.2%, n = 125)	7 (50%, n = 14)	12 (10.8%, n = 111)	<b>0.001</b>
<b>Medication</b>				
ACE inhibitor or ARB (%)	251 (93.7%)	78 (89.7%)	173 (95.6%)	0.11
Beta-blocker (%)	239 (89.2%)	67 (77%)	172 (95%)	<b>&lt;0.001</b>
Mineralocorticoid receptor antagonist (%)	123 (45.9%)	18 (20.7%)	105 (58%)	<b>&lt;0.001</b>
Loop diuretic (%)	147 (55.1%)	30 (34.5%)	117 (65%)	<b>&lt;0.001</b>
Thiazide (%)	80 (29.9%)	34 (39.1%)	46 (25.4%)	<b>0.03</b>
Oral anticoagulant (%)	90 (33.8%)	19 (22.1%)	71 (39.4%)	<b>0.006</b>
Aspirin or clopidogrel (%)	192 (71.6%)	53 (60.9%)	139 (76.8%)	<b>0.009</b>
Statin (%)	184 (68.7%)	53 (60.9%)	131 (72.4%)	0.07
Digitalis (%)	29 (10.8%)	5 (5.7%)	24 (13.3%)	0.09
<b>Laboratory parameters</b>				
Haemoglobin (g/dL)	13.42 ± 1.51	13.41 ± 1.42	13.42 ± 1.55	0.96
Leucocytes (/nL)	6.94 ± 2.03	6.63 ± 1.76	7.09 ± 2.13	0.1
Platelets (/nL)	222.62 ± 68.77	223.12 ± 52.38	222.38 ± 75.52	0.9
Sodium (mmol/L)	141.39 ± 4.04	142.37 ± 3.81	140.92 ± 4.07	<b>0.007</b>
Potassium (mmol/L)	4.49 ± 0.57	4.44 ± 0.51	4.51 ± 0.60	0.6
Creatinine (mg/dL)	1.186 ± 0.43	1.08 ± 0.34	1.24 ± 0.46	<b>0.02</b>
GFR (CKD-EPI, mL/min)	59.66 ± 14.84	62.09 ± 13.59	58.51 ± 15.3	0.1
Serum ferritin (µg/L)	86.54 ± 32.0	90.11 ± 32.86	84.85 ± 31.53	0.2
TSAT (%)	23.53 ± 9.92	25.57 ± 10.58	22.57 ± 9.46	<b>0.02</b>
Transferrin (mg/dL)	270 ± 49.3	257.93 ± 46.14	275.73 ± 49.84	<b>0.006</b>
NT-proBNP (ng/L)	1478 ± 2696	403 ± 498	2113 ± 3219	<b>&lt;0.001</b>
Albumin (g/L)	37.05 ± 3.76	37.26 ± 3.43	36.95 ± 3.91	0.535

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT-D, cardiac resynchronization therapy- defibrillator; CRT-P, cardiac resynchronization therapy- pacemaker; GFR, glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TSAT, transferrin saturation.

lower event rate, muscle wasting did not remain an independent predictor of death after multivariable adjustment, most probably a reflection of the overall low event rate in this cohort.

Data are accumulating to suggest that catabolic wasting processes are present in advanced HF. These probably include activation of pro-inflammatory cytokines, low anabolic drive,<sup>19</sup> growth hormone resistance, and overactivity of the renin-angiotensin-aldosterone system. The net result is loss of functioning skeletal muscle via the ubiquitin-proteasome

system, autophagy, and increased myocyte apoptosis.<sup>4</sup> It is assumed that skeletal muscle as one of the main energy depots of the human muscle is lost earlier than other tissues like adipose tissue or even bone mineral density.<sup>9</sup> However, the latter two are also affected in patients with manifest cachexia in advanced HF in whom tissue loss is so advanced that affected patients are losing body weight. One of the main challenges remains therefore to identify patients early and before weight loss becomes apparent. Our present study underscores the assumption that the loss of skeletal muscle

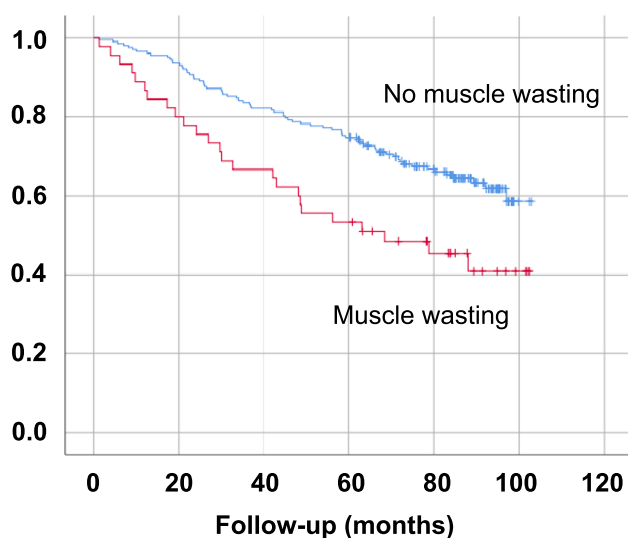
**Table 2** Patients' characteristics by muscle status

	Without muscle wasting (n = 221)	With muscle wasting (n = 47)	P-value
Age (years)	66.12 ± 11.04	71.94 ± 8.60	<b>0.001</b>
Sex (% female)	55 (24.9%)	2 (4.3%)	<b>0.001</b>
Iron deficiency (%)	103 (46.8%)	34 (72.3%)	<b>0.002</b>
Anaemia (%)	59 (26.7%)	22 (46.8%)	<b>0.009</b>
NYHA class	2.29 ± 0.60	2.47 ± 0.72	0.1
GFR (CKD-EPI, mL/min)	59.80 ± 14.93	59.05 ± 14.53	0.8
NT-proBNP (ng/L)	1272 ± 2469	2459 ± 3467	<b>&lt;0.001</b>
Albumin (g/L)	37.26 ± 3.62	36.09 ± 4.27	0.055
Transferrin (mg/dL)	267.81 ± 45.64	280.23 ± 63.29	0.207

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

without manifest weight loss already identifies patients at increased risk of death. Indeed, cardiac cachexia had already been described as an independent predictor of death more than 20 years ago, but it is now becoming clear that skeletal muscle plays a pivotal role in this setting, because patients who lose muscle are unable to exercise to a sufficient degree as highlighted by low quality of life. Apart from those named earlier, mechanisms involve reduced peripheral blood flow,<sup>11</sup> abnormal ergoreflex physiology,<sup>20</sup> and altered nutritional intake,<sup>21</sup> but probably also iron deficiency and anaemia.<sup>22,23</sup> In particular, iron deficiency has been shown to have effects in skeletal muscle, because enzymes of the mitochondrial electron transport chain are iron dependent, and recent data show that iron administration can help to improve phosphocreatine recovery in the muscle.<sup>24</sup>

### Cumulative survival



**FIGURE 1** Kaplan–Meier survival curves by status of muscle wasting in the overall cohort.

Previous studies have aimed to use skeletal muscle mass as a predictor of death in patients with HF but were hampered by methodological problems, sample size, or both. For example, Lopez *et al.*<sup>6</sup> have tried to extrapolate skeletal muscle mass using abdominopelvic computed tomography scans performed during an acute hospitalization in order to diagnose sarcopenia in 160 patients with HF, and they observed a 4.5-fold increase in the risk of death in those patients labelled as sarcopenic. However, it is difficult, if not impossible, to use abdominopelvic imaging to understand appendicular skeletal muscle mass. Recently, this approach has been discouraged, as it may be a 'flawed premise'.<sup>25</sup> Apart from this, the area of interest, psoas muscle, can be assessed by the volume of the entire muscle, its unidimensional thickness, its cross-sectional area either unadjusted in cm<sup>2</sup>, normalized to patient height, normalized to body surface area, or normalized to the area of the adjacent vertebral body.<sup>25</sup> Thus, even though these authors identified low psoas muscle area in patients with chronic HF after an acute hospitalization as an independent predictor of death, these findings should not be extrapolated to the skeletal muscle mass of the extremities. Very similarly, Tsuji *et al.*<sup>5</sup> examined psoas muscle mass in 78 patients undergoing left ventricular assist device implantation. They found that perioperative muscle wasting as extrapolated from the psoas measurement approach was associated with higher mortality in their patient cohort. Nichols *et al.* used DEXA scanning in 60 male patients with coronary heart disease and found that 13 of these (21.7%) had low skeletal muscle mass, as defined using a skeletal mass index <7.26 kg/m<sup>2</sup> or appendicular skeletal mass <25.72%. In this comparatively small cohort of patients without HF, lower skeletal muscle mass was associated with a higher risk of all-cause mortality. Tsuchida and colleagues found a sarcopenia prevalence of 52.6% among 38 patients with acutely decompensated HF but mainly used sarcopenia as a predictor of high BNP levels.<sup>7</sup>

Our findings from patients with HF call for closer scrutiny of skeletal muscle and also for a wider availability of DEXA scanning. As mentioned, previous studies have been hampered by methodological problems, because DEXA scanning is not routinely available in many hospitals. Computed tomography and magnetic resonance imaging are alternatives, but the assessment of appendicular skeletal muscle with these imaging techniques is not common for reasons of radiation exposure, time restrictions, or cost/reimbursement issues. DEXA scanning, on the other hand, is a very quick alternative (scanning time less than 2 min) that provides crucial information about a patient's body composition in the limbs as well as in the whole body. It is comparatively cheap and simple to handle. It remains a matter of speculation if screening tools such as the SARF-F questionnaire or skinfold measurements can identify patients with HF in need of DEXA scanning or other imaging techniques, which would make patient selection even



**Table 3** Single and multivariable Cox proportional hazard models for death from any cause

	All patients				All patients				HFpEF				HFrEF			
	Single-predictor model				Multivariate model				Multivariate model				Multivariate model			
	HR	95% CI	$\chi^2$	P	HR	95% CI	Wald	P	HR	95% CI	Wald	P	HR	95% CI	Wald	P
Age (per year)	1.03	1.01–1.06	9.43	0.002	1.02	0.99–1.05	1.71	0.192	0.98	0.93–1.03	0.94	0.33	1.03	0.99–1.07	3.65	0.056
NYHA (per 1 unit increase)	2.24	1.58–3.18	20.74	<0.001	1.36	0.86–2.16	1.72	0.191	2.03	0.63–6.51	1.40	0.23	1.10	0.63–1.92	0.12	0.729
LVEF (per 1 unit increase)	0.96	0.94–0.97	27.83	<0.001	0.96	0.92–0.99	5.87	<b>0.015</b>	0.91	0.81–1.02	2.84	0.09	0.92	0.91–0.99	5.54	<b>0.019</b>
Creatinine (per 1 unit increase)	2.23	1.60–3.09	23.43	<0.001	1.94	1.12–3.38	5.51	<b>0.019</b>	2.57	1.19–181.54	11.89	<b>0.001</b>	1.34	0.73–2.48	0.89	0.345
Log NT-proBNP (per 1 SD increase)	2.04	1.58–2.62	31.32	<0.001	1.22	0.85–1.75	1.15	0.284	0.88	0.37–2.11	0.08	0.78	0.14	0.94–2.23	2.88	0.090
Iron deficiency (present)	1.62	1.07–2.45	5.27	0.023	1.08	0.64–1.81	0.08	0.772	1.99	0.58–6.82	1.19	0.27	0.91	0.50–1.65	0.09	0.759
Muscle wasting (present)	1.98	1.25–3.13	8.88	0.003	1.80	1.01–3.19	0.04	<b>0.044</b>	1.86	0.32–10.70	0.48	0.48	0.91	0.05–3.71	4.45	<b>0.035</b>
HFpEF vs. HFrEF	0.37	0.22–0.63	14.60	<0.001	0.56	0.20–1.60	1.64	0.281								
					$\chi^2$ model = 60.55				$\chi^2$ model = 29.17				$\chi^2$ model = 32.56			

CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

easier.<sup>26,27</sup> Patients with low skeletal muscle, that is, sarcopenia or at risk of muscle loss (pre-sarcopenia),<sup>28</sup> may benefit from more aggressive HF therapies, because retrospective analyses have highlighted the importance of using standard HF medications like beta-blockers or angiotensin-converting enzyme inhibitors in these patients.<sup>29,30</sup> Additional treatment approaches include exercise training (endurance exercise, muscle strength training, and inspiratory muscle training), nutritional support (e.g. high-calorie nutritional supplements and branched-chain amino acids),<sup>31–33</sup> and possibly anabolic substances.<sup>4,34,35</sup> Unfortunately, none of these interventions have been tested in prospective randomized controlled trials of adequate size so far, but smaller trials suggest that exercise training improves quality of life and the distance covered during the 6 min walk test.<sup>12</sup>

Taken together, muscle wasting beyond the cut-offs defined to identify sarcopenia identifies a large proportion of patients with HF who have low muscle strength, quality of life, and exercise capacity and who are likely to become frail in that they may be at increased risk of falling, risk of fractures, and hospitalizations. Our data show that these patients are also at two-fold increased risk of death, an effect primarily driven by events in patients with HFrEF. Future studies are needed to better understand this effect in patients with HFpEF, because the event rate in this subgroup of our study population remained small.

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## Conflict of interest

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